CONTACT DERMATITIS FROM VITAMIN B_1 (THIAMINE)

Relapse after Ingestion of Thiamine. Cross-sensitization to Co-Carboxylase*

NIELS HJORTH, M.D.

Several hundreds of cases of untoward reactions from thiamine have been reported. They have been described as including asthma, urticaria, shock and even sudden death (1). Apparently, they only occur after injections, often late in a series of treatment with high doses. Most of the reactions can hardly be considered as allergic in nature, but are rather due to intolerance to the pharmacological action of thiamine upon the autonomic nervous system (2). Normally thiamine accentuates the various effects of acetylcholine. As an expression of this property many normal persons show an immediate papular response to an intradermal injection of thiamine (2, 3, 4). Because of this phenomenon many of the reported reactions have erroneously been interpreted as allergic (2). Only in rare instances has it been possible to verify the hypersensitivity by a positive Prausnitz-Küstner's test (3).

Allergic eczematous hypersensitivity to the thiamine has only rarely been reported. Dalton and Pierce (5) found positive patch tests to thiamine in 10 workers employed by a pharmaceutical factory in handling this material. It is not apparent from the report, whether the thiamine was the actual cause of eczema. In a similar firm, Rajka and Vincze (6) found that the major cause of eczemas occurring among workers employed in the synthesis of aneurin was one of the intermediate compounds in the synthesis of thiamine (viz. ethoxymalodinitril). Only one of their cases showed at the same time a hypersensitivity to pure thiamine. Another of the thiamine precursors, chlorpyrimidine, was the cause of a Danish case of occupational dermatitis (7), with positive patch tests to crude thiamine, but negative reactions to purified thiamine from the same factory.

Sensitization from contact solely with pure thiamine has only been reported once (8). The patients were two women, who were employed in filling vials with thiamine solution and during this work had developed a nummular eczema of both hands. Patch tests to pure aneurin were positive, and the etiology was further confirmed by the observation that relapse occurred after the work was resumed.

These two cases are similar to the one reported below. The investigation in the present case, however, has supplied details which supplement the scanty knowledge of this peculiar hypersensitivity.

THIAMINE

As shown in table 1 the molecule comprises a thiazole and a pyrimidine component. The hydrochloride forms a stable solution of pH 3. When the pH is increased above 5 the thiamine may be split by heating or ultraviolet radiation into the thiazole and the pyrimidine components (9).

After intestinal resorption the thiamine is esterified with pyro-phosphoric acid and thus changed to co-carboxylase, which is a co-enzyme in the cellular metabolism. Part of the ingested thiamine is eliminated in the urine as a pyrimidine derivative (9). In sweat, even after excessive doses, only minimal amounts are excreted (10).

The daily optimal intake is stated to be 1–3 mg per day. In Denmark this is effected by thiamine fortification of flour. The average intake from this source averages 1–2 mg. per day.

CASE HISTORY

F. m. L. 303819. A 17 years old factory girl, who had suffered from eczema in infancy, but had otherwise been healthy.

In May 1955 she was employed at a pharmaceutical firm, where she filled vials with different vitamin preparations. After 4 months work an eczema appeared on the fingers, the dorsum of the hands, and the wrists. Later she developed a perioral eczema. During a short absence from the work the eczema disappeared, only to recur when she resumed. By the end of October she was referred for dermatological treatment.

Routine patch tests showed a hypersensitivity to bichromate, but no chromate contact could be ascertained. Several laboratory chemicals, including phenol and benzyl alcohol gave negative

* From Finseninstitutet, Dept. of Dermatology, Copenhagen. (Chief: Professor P. V. Marcussen.)

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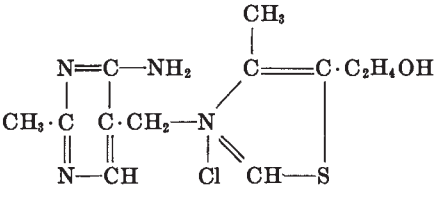
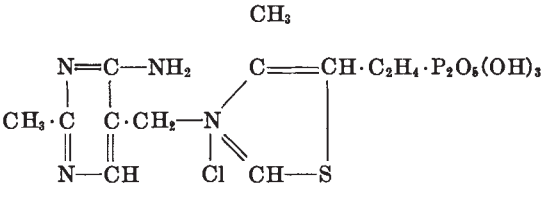
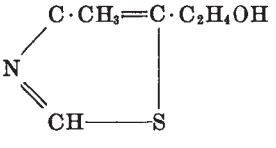
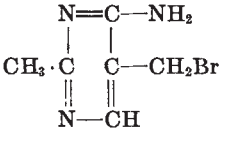
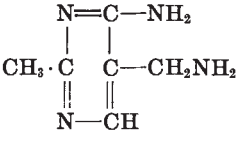
TABLE 1

Patch Tests

Results of patch tests with components and derivatives of thiamine. Water was used diluent. Patch tests were left for 48 hours and read after 48 and 72 hours. 1+ erythema, 3+ erythema, infiltration, vesicles.

Substance	Date	Conc.	Reaction
Thiamine 	11/4/55	Pure	+
	11/7/55	10%	+++
	11/17/55	1%	+++
		0.1%	+
		0.01%	−
	2/11/56	0.1%	+
Co-Carboxylase 	2/13/56	10%	+++
		1%	+++
		0.1%	−
4-methyl-5-(oxyethyl)-thiazole 	2/13/56	Pure	−
		10%	−
2-methyl-6-amino-5-*brom-methyl-pyrimidine** 	2/11/56	Pure	+++
		10%	+++
	2/13/56	10%	−
		1%	−
2-methyl-6-amino-5-*amino-methyl-pyrimidine* 	2/11/56	Pure	−
		10%	−
Sulfathiazol-cream	11/17/55	5%	−
Sulfapyrimidine (Sulfadiazine)	2/13/56	Pure	−

* A primary irritant.

The substances employed for patch testing were kindly supplied by Hoffmann-la Roche Ltd.

reactions. Further patch tests with occupational contactants led to the demonstration of positive reactions to thiamine, even in a 0.1% dilution. The patient had sometimes been employed filling vials with thiamine and had noticed irritation of the skin during this work. She further supplied the information that she daily took a tablet of vitamin B. This was found to contain 1 mg. of thiamine.

Under conservative treatment the eczema disappeared after a few months. Afterwards the patient changed her occupation and from January

1, 1956 she worked as a domestic servant employed in dishwashing and cleaning without experiencing any further irritation of the skin. She had no contact with thiamine and took no vitamin B tablets. After 6 weeks she returned for a follow up examination, which disclosed only residual traces of lichenification of the former patches of eczema.

Experimental provocation: In the period of treatment during which the patient continued her work, a sudden flare-up of the eczema was observed twice. On the first occasion it was revealed that the patient, on her own initiative, had resumed work filling thiamine vials.

The second time, the eczema flared up as a result of experimental provocation. In order to examine the effect of ingested thiamine two coated tablets of 100 mg. thiamine each were administered on the 6th of December 1955. Next day the almost healed patches of eczema were red and itching. An additional 100 mg. of thiamine was administered in a coated tablet. The same day she had an acute relapse to the state prior to treatment, but after a week the eruption faded.

A similar relapse occurred 2 months after the eczema had disappeared. At the control examination on the 11th February 1956 supplementary patch tests, scratch- and intracutaneous tests were performed (cf. table 1). Patch tests with thiamine were positive as previously, and a cross-reaction to co-carboxylase was demonstrated. Intracutaneous tests with 0.1 ml. of 0.1% solutions of thiamine and co-carboxylase were negative. 4 days later similar intracutaneous tests with 0.1 ml. of 1% solutions and half an hour later with 10% solutions of the same substances were performed (total dose of thiamine co-carboxylase 22 mg.). The four injections all provoked immediate papular response, as is the case in many normal persons.

Between 6 and 10 hours after the injections a pruritic area of erythema appeared around the mouth. Shortly after both hands and wrists were similarly involved. Next day the pruritus had subsided, but an intensely red, vesicular dermatitis was found in all the formerly affected areas. The 5 day old patch tests showed no focal reactions, but late papular reactions of 20 by 20 mm., without vesicles, had appeared at the sites of the intracutaneous injections with thiamine 1% and 10%, while the co-carboxylase had given a doubtful reaction.

Under treatment with zinc oxide lotion the dermatitis disappeared with scaling within ten days.

TABLE 2

Reactions to thiamine solutions of different pH. Intradermal tests with 0.05 ml. in 20 patients.

	pH	Wheal, mm	
		Average	Range
Thiamine HCl, 4%	3	11.25	9.5–13.5
Thiamine, 4%	5.6	10.25	7–13.5

CONTROLS

Consecutive dermatological patients served as controls.

Patch tests with thiamine 50% in water and with co-carboxylase 1% in water were negative in 100 patients. Patch tests with pure methyl-amino-bromomethyl-pyrimidin (cf. table 1) were done on 34 patients of which 6 showed positive reactions clinically of the primary irritancy type. All had negative reactions to a 10% solution (and to thiamine). Later 122 patients were tested with a 10% solution of the same pyrimidine derivative. One patient showed a positive eczematous reaction to a 10% and a 5% solution, but negative reaction to thiamine. The cause of the positive reaction could not be ascertained.

Intracutaneous tests with thiamine confirmed that this substance normally produces a wheal and a flare. If 5% and 10% solutions are employed such reactions are often accompanied by pseudopods.

Similar reactions may, however, be provoked in many normal persons by intracutaneous tests with 1% acetic acid which has about the same pH as a thiamine solution.

In order to determine whether the whealing effect of thiamine might be due to the low pH of the solutions, the reactions to a 4% solution of thiamine were compared to those of a thiamine solution of pH 5.6. The latter solution was prepared by mixing equal parts of a 2 normal NaOH with an 8% solution of thiamine. Owing to the instability of thiamine at the resulting pH of 5.6 the solution was prepared immediately before use and discarded after 60 minutes. The results (cf. table 2) confirmed that the reactions are due to some specific action of thiamine.

The whealing after intracutaneous injections of thiamine is generally attributed to an enhancing effect upon the cholinergic nervous system (2, 4). In two patients, however, with cho-

linergic urticaria and a verified high sensitivity to cholinergic substances, intracutaneous reactions to thiamine did not show any peculiarities.

Intracutaneous tests with co-carboxylase 1% 0.05 ml. were performed in 30 patients and showed in 25 cases a wheal ranging from 5 to 14 mm. accompanied by a flare up to 40 mm. The flare remained for more than 20 minutes. 5% and 10% solutions provoked similar reactions but left a central necrosis, probably owing to the strongly acid reaction (pH 1.5–1.8).

DISCUSSION

Of special interest in the present case is the relapse of eczema provoked by the ingestion of thiamine. Dalton and Pierce (5) administered thiamine by mouth, in unstated dosage, to ten patients with positive patch tests to aneurin. No "untoward signs or symptoms resulted." In the present case the eczema relapsed after ingestion of a dose of thiamine far above the physiological requirements, but of a size used therapeutically. However, the dose of tolerance could not be determined owing to the reluctance of the patient to permit further tests.

It is particularly striking that a vitamin which normally plays an essential part in cellular metabolism should have antigenic properties. So it might be presumed that the primary allergen is an impurity, possibly a decomposition product, which under occupational conditions of exposure, might occur in sufficient concentration for sensitizing.

Impurities, however, could not explain the hypersensitivity in the present case, where patch tests with pure crystalline preparations from different sources (Merck; la Roche) were all positive.

The decomposition products have not been tested in any of the previously reported cases of hypersensitivity to thiamine. Sensitization to these products might occur since thiamine is unstable at the prevailing pH of the skin surface.

Patch tests with the pyrimidine-component of thiamine pure and in 10% solutions were positive, but repeated tests with 10% and 1% solutions were negative (cf. table 1). As thiamine elicited positive reactions even in 0.1% solutions, it is unlikely that the decomposition products could be the primary allergen.

Although the pyrimidine derivative employed for the tests is a primary irritant, the reactions provoked by it might be an expression of a cross-sensitization or secondary allergy, provided the pyrimidine part was the antigenic determinant group of the thiamine molecule. This cross-sensitization should, however, have included the amino-methyl-pyrimidine, which was tested but with a negative result. Thus the observed reactions from the bromo-methyl-pyrimidine must have been due to the primary irritant properties of the substance, and it may be concluded that the primary allergen in this case was the whole thiamine molecule.

Considering the chemical structures it is understandable that a cross-reaction to co-carboxylase could be demonstrated. This is, however, of some theoretical interest, as it seems to be the first demonstration of a hypersentitivity to a pure co-enzyme.

SUMMARY

1. A case of occupational dermatitis from thiamine is reported. Relapses of the eczema occurred after ingestion of thiamine (200 mg.) and later after intracutaneous injection of 10 mg thiamine.

2. Patch tests with the components indicated that the antigenic determinant was the whole molecule.

3. A secondary allergy to co-carboxylase was demonstrated.

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